BBA - Reviews on Cancer 1870 (2018) 151–157

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

Hybrid epithelial/mesenchymal phenotype(s): The 'fittest' for metastasis?

Mohit Kumar Jolly[a], Sendurai A. Mani[b,*], Herbert Levine[a,b,*]

[a] Center for Theoretical Biological Physics, Rice University, Houston, TX, USA
[b] Department of Translational Molecular Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

ARTICLE INFO

Keywords:
Hybrid epithelial/mesenchymal
Collective cell migration
Circulating tumor cells
Metastasis
Epithelial-mesenchymal transition

ABSTRACT

Metastasis is the leading cause of mortality among cancer patients. Dissemination enabled by an epithelial-to-mesenchymal transition (EMT) of carcinoma cells has long been considered to be the predominant mechanism for carcinoma metastasis, based on overexpression studies of many EMT-inducing transcription factors. Individual CTCs – and a binary framework of EMT – have been long considered to be sufficient and necessary condition for metastasis. However, recent studies have shown that collective migration and invasion through tumor buds and clusters of Circulating Tumor Cells (CTCs) as possibly being the prevalent mode of metastasis, although individual CTCs may still contribute to metastasis. These strands and clusters have been proposed to often exhibit a hybrid epithelial/mesenchymal (E/M) phenotype where cells retain epithelial traits of cell-cell adhesion and simultaneously gain mesenchymal characteristics of migration and invasion. To highlight the crucial questions regarding metastasis, we define EMT in a non-binary and context-specific manner, suggest that it can be viewed as a trans-differentiation process, and illustrate the implications of hybrid E/M phenotype(s) and cluster-based dissemination in metastasis.

1. Introduction

Despite major advances in diagnosis and treatment of cancer, metastasis and development of resistance to chemo and targeted therapies continue to be challenging and in the end cause over 90% of all cancer-related deaths [1]. Genetic transformations can, undoubtedly, contribute to these challenges by enabling various hallmarks of cancer. In addition, however, surviving in and leveraging an ever-changing microenvironment to their advantage requires cancer cells to be highly phenotypically plastic. Epithelial-Mesenchymal Transition (EMT) and the reverse Mesenchymal-Epithelial Transition (MET) are canonical examples of cellular plasticity implicated in metastasis and therapy resistance.

EMT and MET were initially identified as keystones of embryonic development; they were shown to give rise to mesoderm and neural crest cells, regulate gastrulation, and mediate formation of multiple organs [2]. This concept was then laterally transferred to study carcinoma metastasis, where EMT was proposed to launch individual cancer cells into the blood circulation, a subset of which would successfully reach distant sites, regain their epithelial traits *via* MET, and colonize to establish macrometastases [3–6]. This binary framework served as a powerful concept for a long time, virtually defining EMT as a necessary and sufficient condition for metastasis.

Recent investigations in embryonic development, tissue repair, and pathological contexts such as fibrosis and cancer metastasis have argued that EMT need not be 'all-or-none' processes, rather cells can transiently acquire partial plasticity and attain hybrid epithelial/mesenchymal (E/M) phenotype(s). Collective cell migration during branching mammary morphogenesis and wound healing have witnessed hallmarks of such partial plasticity [7]. Similarly, metastasis can also be achieved *via* collective cell migration [8,9] by cells that retain at least partially their epithelial traits such as cell-cell adhesion. Consistently, a recent *in vivo* study showing spontaneous EMT highlighted that cells could exist stably in distinct hybrid E/M phenotype(s) and these hybrid phenotypes were more metastatic as compared to those in an extreme mesenchymal state (*i.e.* the other end of the binary framework) [10]. Thus, in this review, we examine EMT in a more nuanced way.

2. Defining EMT mechanistically

EMT is a multi-dimensional complex cellular program involving changes in one or more of these traits – cell polarity, cell-cell adhesion, motility, and invasion – and changes in levels and/or localization of canonical markers such as E-cadherin [11]. In the simplest terms, EMT can be viewed as a process where epithelial traits are lost concomitantly

* Corresponding authors at: Center for Theoretical Biological Physics, Rice University, Houston, TX, USA; Department of Translational Molecular Pathology, University of Texas MD Anderson Cancer Center, Rice University, Houston, TX, USA.
E-mail addresses: mani@mdanderson.org (S.A. Mani), herbert.levine@rice.edu (H. Levine).

https://doi.org/10.1016/j.bbcan.2018.07.001
Received 5 April 2018; Received in revised form 18 June 2018; Accepted 2 July 2018
Available online 08 July 2018
0304-419X/

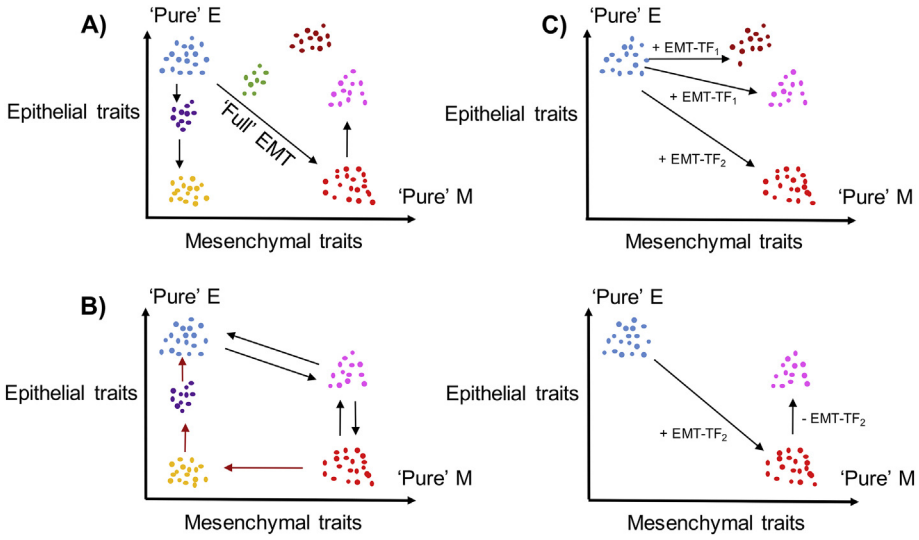

Fig. 1. Epithelial-mesenchymal plasticity as plotted on a reduced 2-dimensional landscape. A) Cells may undergo varying levels of changes in their epithelial and/or mesenchymal traits, thus giving rise to various subpopulations (shown by different colors), each of which manifests a different flavor of partial EMT. B) Cells undergoing MET may (black arrows) or may not (brown arrows) follow the same trajectory as cells undergoing EMT do. C) (top) EMT induction by the same induction signal/EMT-TF may drive cells to different extents of EMT, depending on factors such as epigenetic status of the cell. Also, different EMT-TFs may have distinct effects. (bottom) Withdrawing the induction/EMT-TF signal may not always lead the cells back to their initial condition.

with gain of mesenchymal traits. During this process, cells may take different paths in this multi-dimensional landscape and encounter one or more distinct intermediate phenotype(s). This trait has been observed in Circulating Tumor Cells (CTCs) in breast and prostate cancer patients [12,13], where both individually migrating CTCs and clusters of CTCs can co-express various epithelial and mesenchymal markers to different degrees [13–16]. Single-cell co-expression of these markers has also been reported in multiple cell lines belonging to lung cancer, prostate cancer, colorectal cancer, ovarian cancer [17–21], and in primary tumors, mouse models, and metastases [22].

In fact, many cells may not undergo a complete EMT and stably attain these intermediate or hybrid E/M phenotype(s) (Fig. 1A) [22]. Stable existence and/or maintenance of hybrid E/M phenotype(s) was proposed initially through computational modelling of EMT regulatory networks [23–26], and validated later *in vitro* in multiple contexts [24]. Recently, the existence of distinct stable hybrid E/M phenotype(s) was demonstrated *in vivo* [10]. These distinct hybrid E/M phenotype(s) – each with characteristic transcriptional signatures – may be visualized as different 'valleys' in a multi-dimensional landscape that cells can stay in for varying amounts of time. Moreover, cells may follow a different trajectory in this high-dimensional landscape while undergoing MET, as compared to while undergoing EMT. Thus, EMT and MET need not be symmetric processes [23] (Fig. 1B).

EMT can be induced by a variety of biochemical and mechanical signals that can impinge on a set of 'EMT-transcription factors' (EMT-TFs) – SNAI1/2, ZEB1/2, FOXC2, PRRX1, GSC, TWIST1/2 – that orchestrate the above mentioned molecular and biophysical changes. Similarly, overexpression of MET-TFs such as GRHL2, ELF3, and ELF5 can drive MET [27]. However, a comprehensive mapping relating various molecular and biophysical aspects of EMT with these EMT-TFs remains far from complete. This mapping is highly likely to be many-to-many; for example, TWIST upregulation may enhance invasion but not always migration [28], and ectopic expression of SNAI1 increases invasion and migration, but does not always induce N-cadherin expression [29]. Further, quantitative differences among the induction of EMT/MET by different EMT/MET-TFs can arise from variations in genetic background, epigenetic state and/or micro-environment (*e.g.* how poised a cell is to undergo EMT/MET), strength of regulation (*e.g.* how strongly can an EMT/MET-TF bind to regulatory regions of its targets), and crosstalk among these different dimensions of EMT (*e.g.* how changes in cell-cell adhesion affects cell invasion) (Fig. 1C, top). For example, overexpression of GRHL2 was sufficient to drive MET in carcinoma cells such as MDA-MB-231, but not in sarcoma cells such as RD and 143B, largely due to differences in chromatin structure [30]. Moreover, the withdrawal of an EMT-TF/EMT-inducing signal may not always restore the exact same cell state prior to its overexpression/treatment [31], for example, cells may undergo only a partial MET [32] (Fig. 1C, bottom). All these aspects depend on the relevant biological context, thus calling for a context-specific mechanistic definition of EMT and MET. This appreciation will also help us rigorously identify the number and relative stability of hybrid E/M state(s) and their implications in tumor progression.

3. Role of EMT and EMT-TFs in mediating metastasis

Exogenous overexpression of many EMT-TFs was shown to enhance migration and/or invasion of cancer cells *in vitro* [33,34], and enhance metastasis *in vivo* [35,36]. This overexpression may trigger one or more metastasis-promoting modes: individual migration, collective migration leading to formation of clusters of Circulating Tumor Cells (CTCs), cooperation among E and M tumor cells, and may even fix some cells in a mesenchymal state. Of course, direct genetic manipulation is not essential. Cells in MMTV-PyMT mice migrate individually or as streams following each other's paths, without any experimental induction of EMT [37]. MMTV-PyMT is a transgenic mouse model to study breast cancer metastasis, where the long terminal repeat (LTR) of mouse mammary tumor virus (MMTV) drives the expression of polyoma virus middle T-antigen (PyMT). Most MMTV-PyMT mice show multifocal tumors in mammary glands and lung metastases [38]. CTCs in this mouse model have both E-cad^{HI} and E-cad^{LO} subpopulations, and E-cad^{LO} cells display typical molecular changes associated with EMT. It therefore seems reasonable to conclude that some aspects of EMT activation were potentially playing a role in their metastatic cascade [37].

EMT may be sufficient for migration and invasion, but is it necessary? It is important to note that breast cancer cells in tumor organoids can invade collectively without displaying a significant (defined as greater than two-fold change) upregulation of canonical EMT markers [39]; it appears to mean that motility can occur in cells that remain molecularly epithelial. This observation is often put together with recent lineage tracing results that showed that knocking down or out of an EMT-TF need not significantly alter metastatic load in those mouse models [40,41]. Put together, these indicate that metastasis may be achieved without an overt activation of EMT-TFs. However, these lineage tracing experiments typically focus on only one EMT-TF and it seems too simplistic to assume that knocking out or down of one EMT-TF prevents all cells in the tumor from undergoing any molecular or morphological changes related to EMT [42,43].

In this regard, cells undergoing EMT often acquire other traits that could contribute to colonization, such as stemness (tumor-initiation potential). EMT was shown to enhance stemness initially in breast

cancer [44]; accumulating evidence later gathered in other carcinomas as well [45]. Recent studies that consider EMT as a non-binary process revealed hybrid E/M cells to be more stem-like or metastatic as compared to epithelial or mesenchymal ones both *in vitro* and *in vivo* [10,46–50]. These observations reinforce the notion that cells that get locked into a mesenchymal state may lose their ability to initiate a tumor; consequently, inhibition of a full-blown EMT may be required for colonization [50–52]. Consequently, 'stemness' need not be a cell-intrinsic property, but a dynamic trait that the cells can acquire or lose, based on their microenvironment [53–55]. As a result, cells in varying EMT phenotypes can display 'stemness' (for instance, mesenchymal-like CD44 + /CD24- and hybrid E/M ALDH +), and potentially interconvert too [56–58]. These subsets of CSCs expressed varying levels of different EMT-TFs [56], and were observed at different spatial coordinates - ALDH + CSCs in the tumor interior, whereas CD44 + /CD24- at the invasive front [57]. Thus, the essential criteria for aggressive behaviour need not be a particular phenotype, but rather enhanced cellular plasticity, as is observed for hybrid E/M cells [46,59], but may be allowed by other pieces of the cell's phenotypic machinery.

An open question that remains is whether cells need to undergo full MET to germinate secondary tumors. Lineage -tracing *in vivo* studies using transcriptional (measuring E-cadherin and Vimentin) and post-transcriptional (measuring alternative splice isoforms of FGFR2) markers of MET have provided evidence for both MET-dependent and MET-independent metastases [60]. Similar to the case with EMT [61], molecular MET and morphological MET may not always happen simultaneously. Thus, we believe that a continued and careful investigation of the roles of EMT/MET and EMT/MET-TFs in establishing functional traits are needed to understand their role in metastasis.

4. EMT as an engine of cellular plasticity and its association with other cellular traits

It would be nice if all existent data fit into this picture, but there are other factors obfuscate the contribution of EMT and/or EMT-TFs to metastasis – pleiotropic and/or non-cell autonomous effects of EMT-TFs.

First, there are non-cell autonomous roles of EMT-TFs that may accelerate metastasis. For instance, ZEB1 or SNAI1 can activate IL-6 and IL-8 transcriptionally [62,63]; these pro-inflammatory cytokines can also induce EMT and other associated traits such as stemness in nearby cells [64], thus indicating how EMT-TFs can exhibit non-cell-autonomous effects and alter the tumor microenvironment (TME) to be more aggressive. Dynamics of TME can, in turn, also allow passive shedding of cancer cells into the circulation instead of postulated active migration and invasion by cells undergoing EMT [11].

Other non-cell autonomous effects of EMT have been reported recently. For instance, ZEB1 can regulate levels of members of the lysyl oxidase (LOX) family of enzymes such as LOXL2 that can crosslink and stabilize collagen deposition, thus increasing matrix stiffness [65]. Stiffer matrices can, in turn, promote EMT through the TWIST1-G3BP2 mechano-transduction pathway [66]. Similarly, ZEB1 can activate hyaluronic acid synthase 2 (HAS2) that can produce increased levels of hyaluronan/hyaluronic acid (HA), which can, in turn, promote EMT by interacting with its receptor CD44 [67,68]. Furthermore, HMLER cells overexpressing Twist or Snail (HMLER-Twist/HMLER-Snail) cells, when co-cultured with control HMLER cells, can impart metastatic traits to the latter through paracrine Hedgehog (Hh) signalling [69]. Such autocrine and/or paracrine feedback loops among tumor cells can aggravate malignant progression in multiple ways, and is reminiscent of reported cooperation among epithelial (E) and mesenchymal (M) cells *in vivo* – while M cells can degrade the surrounding matrix leading to invasion and intravasation, E cells can colonize distant organs [70].

These studies compel us to revisit the conclusions drawn from lineage-tracing studies claiming the dispensability of EMT for metastasis. A lack of fate-mapped cells in circulation and at the metastatic site led the authors to argue that EMT was not required for metastasis [40,41]. However, these studies do not rule out the possibility that M cells may have enabled the E cells to reach the metastatic site by triggering such non-cell autonomous aspects. These conclusions, thus, largely overlook any emergent effects of cooperation among different subpopulations. Evidence for such cooperation has been mounting - recent *in vitro* experiments using heterogeneous cell line HMLER (that contain E and M subpopulations) demonstrate that a mixture of E and M cells form many more mammospheres as compared to either subpopulation alone [71]. This cooperation may even contribute to the enhanced metastatic potential of polyclonal clusters of CTCs as compared to the individually migrating CTCs.

Second, many EMT-TFs have pleiotropic roles beyond regulating migration and/or invasion that may contribute to metastasis. For example, ZEB1 drives resistance against cisplatin in ovarian carcinoma, activates DNA damage response to promote resistance against radiation in breast cancer, and associates with resistance to erlotinib in non-small cell lung cancer (NSCLC) [62]. miR-200/ZEB axis can also lead to CD8 + T-cell immune-suppression by mediating the levels of PD-L1 [62] and immunoproteasome that facilitate antigen presentation for CD8 + T-cell response [72]. Similar roles have been observed for other EMT-TFs such as FOXC2 [73]. Importantly, the resistance against multiple therapies that is driven by EMT-TFs need not be channelled through their induction of EMT, for instance, EMT itself may not be causing resistance against radiation, but ZEB1 plays a causal role thereby stabilizing CHK1 – a critical effector kinase in DNA damage response [74].

The abovementioned pleiotropic roles of EMT-TFs may enable different hues of cellular plasticity. For instance, plasticity in switching between different metabolic modes – glycolysis and oxidative phosphorylation – strongly depends on the levels of ZEB1 in pancreatic cancer and in high-grade serous ovarian cancer (HGSOC) [75,76]. Similarly, the activation of glucose transporter GLUT3 by ZEB1 can be independent of its role as an EMT-TF [77]. Furthermore, the transition from a non-CSC to CSC state is based on a bivalent chromatin status of the ZEB1 promoter that contains both activating (H3K4me3) and repressive (H3K27me3) marks, but not explicitly on its ability to repress epithelial genes and/or promote mesenchymal ones during EMT [62]. Finally, ZEB1 can also induce vasculogenic mimicry – a novel vascular pattern formed by cancer cells – *in vitro* and *in vivo* [78]. Thus, it may be more apt to call EMT-TFs such as ZEB1 (and the networks formed by their interactions) as 'motors of cellular plasticity' [79] driving disease progression, instead of referring to EMT as an 'engine of cellular plasticity'.

5. Hybrid E/M phenotype: the 'fittest' phenotype for metastasis?

Promising experimental and clinical results emphasize the implications of hybrid E/M phenotype(s) in fostering carcinoma metastasis [22]. First, hybrid E/M phenotype(s) perhaps exhibit maximum plasticity and can traverse the spectrum of phenotypes along the EMT axis – as indicated by both computational and experimental analyses [22,59] – while 'fully' epithelial and mesenchymal phenotypes may be locked in by various factors including epigenetics. When E, M and hybrid E/M subpopulations of PKV cell line (established from CPKV prostate cancer mouse model) were segregated and cultured separately *in vitro* for two weeks, approximately 80% E and M cells retained their phenotype, but only 10% hybrid E/M were able to do so; the remaining 90% convert to E or M [59]. This relatively high plasticity of a hybrid E/M phenotype to switch to either E or M state may abet different steps of the metastatic cascade. While E cells may be limited in their ability to intravasate by themselves, and M cells may require exogenous signals to activate MET and cell proliferation to colonize, hybrid E/M cells moving collectively may not face such heightened rate-limiting steps during metastasis (Fig. 2) – an extremely inefficient process with remarkably high attrition rates [80].

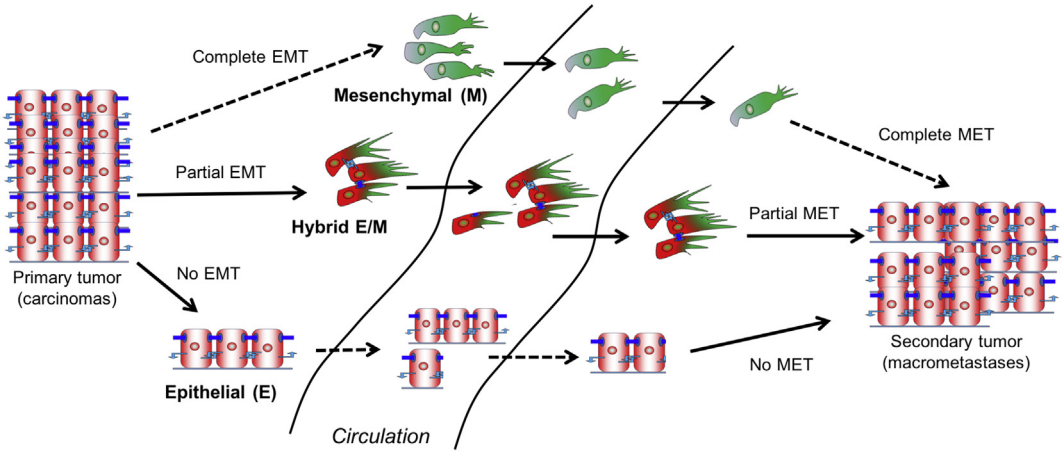

Fig. 2. Metastatic potential of E, M, hybrid E/M phenotypes. Hybrid E/M cells seem to represent the 'fittest' phenotype for successful metastasis, as they do not tend to face the limiting steps (represented by dotted lines) that E and M cells may typically encounter.

Second, hybrid E/M phenotype(s) exhibit enhanced stemness/tumor-initiating traits *in vitro* and *in vivo* [10,46,81]; consistently, co-expression of E and M markers correlate with poor clinical outcome across breast cancer subtypes [46], and in other cancers [22,82]. Enhanced plasticity of hybrid E/M phenotype(s) to convert to E and M cells – that may then cooperate – can be expected to underlie its amplified tumor-initiation ability [71]. Thus, EMT may be viewed as a trans-differentiation process where E and M cells interconvert by passing through an intermediate 'stem-like' state. This conceptual framework can help explain the observed multi-lineage differentiation potential of cells undergoing EMT [83]. Third, hybrid E/M phenotype(s) can be more anoikis-resistant [84], potentially facilitating survival of CTCs in a hybrid E/M phenotype, as observed in aggressive breast and prostate cancer cases [12]. Fourth, hybrid E/M cells can be equally, if not more, therapy-resistant than cells undergoing a complete EMT - a hybrid E/M phenotype can also exhibit resistance against erlotinib in NSCLC [85], against paclitaxel, salinomycin, and paclitaxel in squamous cell carcinoma [86], and against HDAC inhibitors in breast cancer [14]. Furthermore, chemotherapeutic drugs and HDAC inhibitors can drive adaptive resistance by inducing and/or selecting for a hybrid E/M phenotype [14,47]. A detailed comparison of IC50 values for various drugs for a hybrid E/M *vs.* mesenchymal population would quantitatively map the relationship between EMT and drug resistance, and help patient classification for treatment strategies. Sixth, while cells undergoing a complete EMT may induce cell cycle arrest [87,88], partially mesenchymal cells may maintain their proliferative potential [89], hence executing a 'go-and-grow' instead of a 'go-or-grow' program.

Finally, cell-cell communication and spatial proximity among hybrid E/M cells can drive the formation of clusters of CTCs [14] – the chief 'villains' of the metastatic cascade [8,9]. For instance, computational models predicted the role of Notch-JAG1 signalling in forming the clusters of CTCs [90], and JAG1 was indeed observed to be among top differentially expressed genes in cluster-based dissemination [9].

CTC clusters, *i.e.* groups of two or more aggregated CTCs, possess several survival advantages. First, cell-cell cooperation among tumor cells may provide pro-survival signals through junctional adhesions [14]; deleting plakoglobin – a key component of adherens junctions – reduces cluster formation and metastases in mice [8]. Second, cell heterogeneity (epithelial *vs.* mesenchymal) can offer competitive advantage during colonization [71], as it can allow for metastasis of different subsets of Cancer Stem Cells (CSCs) [56,57]. Third, heterotypic clusters containing immune or stromal cells may help in evading immunosurveillance both in circulation and at the metastatic site(s) [91]. Moreover, stromal cells and cancer cells can indulge in metabolic symbiosis [92], thus fuelling tumor growth. Fourth, clustered cells may survive mechanical stresses and resist anoikis more efficiently, and navigate more effectively in response to any chemical gradients [93,94]. Finally, clusters can be passively shed and get trapped in blood vessels, thus obviating the need for a full-blown EMT to complete the metastatic cascade [11]. The abovementioned advantages yield insights into mechanisms associating shorter progression-free survival and overall survival with CTC clusters [91]. Intriguingly, the prognostic significance of clusters of CTCs were reported even before EMT was identified as a developmental biology phenomenon [22].

6. Areas for future investigation

Many open questions remain in precisely identifying the cellular and molecular traits of hybrid E/M phenotype(s) and clusters of CTCs that ascribe to them their enhanced metastatic potential. The number and relative stability of hybrid E/M phenotype(s) need to be described rigorously, and more importantly, their metastatic implications should be unambiguously investigated. Extreme care should be practised before labelling any or every individual cell co-expressing a few epithelial and mesenchymal markers as a hybrid E/M phenotype, or, more crucially, calling any heterogeneous carcinoma cell population as a manifestation of 'partial EMT' so as to prevent the emergence of a dogma that establishes 'partial EMT' as a necessary and sufficient condition for metastasis. Further, the bidirectional feedback between molecular (gene expression) and morphological (cellular biophysics) aspects of EMT [61] requires a quantitative meticulous characterization through using integrated computational-experimental approaches [21,95,96]. Such efforts can elucidate the context-dependent mapping between molecular states of EMT and corresponding biophysical traits such as invasion and migration.

The interplay among multiple facets of cellular plasticity such as EMT, stemness, and altered metabolism is in the process of being deciphered. The differences in metabolism and stemness of individual CTCs *vs.* clusters of CTCs, and other molecular aspects governing drug resistance should be understood better to dissect the role of stromal and immune cells in metastasis. Similarly, microfluidic-based and computational simulation of clustered migration coupled with real-time *in vivo* microscopy capturing different stages of the metastasis-invasion cascade are capable of unravelling these unresolved open biological questions and eventually guide clinical studies for stratification and personalization of therapeutic decisions [91].

Next, molecular mechanisms driving heightened metastatic potential of CTC clusters need further investigation. CTC clusters can not only provide survival signals to one another, but also may contain cells with dynamically varying EMT phenotypes that can cooperate in forming metastasis. Cell lines that grow as clusters in suspension can be used as surrogate for identifying the diagnostic, prognostic, and clinical

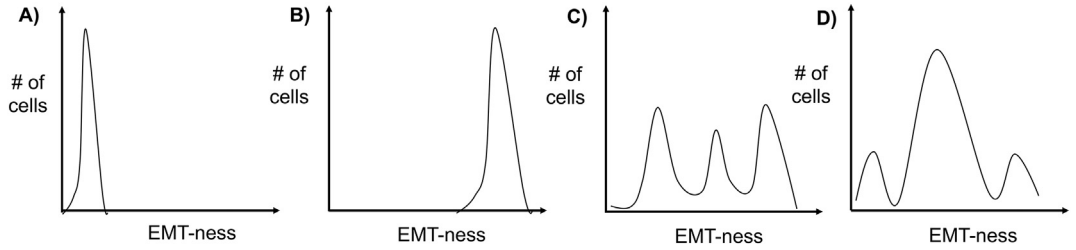

Fig. 3. Different possible distributions of different subpopulations of cells in tumors. A, B) A homogeneous cell distribution in terms of their EMT-ness (on either end of the spectrum). C, D) A heterogeneous cell distribution with varying proportions of E, hybrid E/M and M subpopulations.

relevance of CTC clusters [15]. Similarly, *in vitro* and *in vivo* assays of stemness, metastasis, and drug resistance using a co-culture of E, M, and hybrid E/M cells in varying ratios can answer crucial questions about cooperation and competition among these subpopulations in executing various steps of cancer metastasis and tumor relapse. These questions help visualize the metastasis-initiating cells as dynamic adaptive entities. Because no unique specific mutational signature has yet been identified for metastasis, despite extensive efforts [54], investigating the design principles of metastasis from the lens of non-genetic heterogeneity [96,97] may be valuable. With increasing use of single-cell RNA-seq [98,99], we should investigate what is worse from a clinical standpoint: a) more or less cells undergoing EMT overall, b) more cells in a hybrid E/M phenotype, or more heterogeneity in the extents to which cells undergo EMT? (Fig. 3).

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

This work was supported in part by the National Science Foundation NSF PHY-1605817 (SAM, HL) and Center for Theoretical Biological Physics (NSF PHY-1427654). MKJ has a training fellowship from the Gulf Coast Consortia on the Computational Biology Training Program (CPRIT grant no. RP170593).

References

[1] E. Ben-Jacob, D.S. Coffey, H. Levine, Bacterial survival strategies suggest rethinking cancer cooperativity, Trends Microbiol. 20 (2012) 403–410.
[2] J. Lim, J.P. Thiery, Epithelial-mesenchymal transitions: insights from development, Development 139 (2012) 3471–3486, https://doi.org/10.1242/dev.071209.
[3] J.P. Thiery, Epithelial-mesenchymal transitions in tumour progression, Nat. Rev. Cancer 2 (2002) 442–454, https://doi.org/10.1038/nrc822.
[4] J.M. Lee, S. Dedhar, R. Kalluri, E.W. Thompson, The epithelial–mesenchymal transition: new insights in signaling, development, and disease, J. Cell Biol. 172 (2006) 973–981, https://doi.org/10.1083/jcb.200601018.
[5] C.L. Chaffer, R.A. Weinberg, A perspective on cancer cell metastasis, Science 331 (2011) 1559–1564, https://doi.org/10.1126/science.1203543.
[6] C. Scheel, R.A. Weinberg, Cancer stem cells and epithelial-mesenchymal transition: concepts and molecular links, Semin. Cancer Biol. 22 (2012) 396–403, https://doi.org/10.1016/j.semcancer.2012.04.001.
[7] M.A. Nieto, R.Y. Huang, R.A. Jackson, J.P. Thiery, EMT: 2016, Cell 166 (2016) 21–45, https://doi.org/10.1016/j.cell.2016.06.028.
[8] N. Aceto, A. Bardia, D.T. Miyamoto, M.C. Donaldson, B.S. Wittner, J.A. Spencer, M. Yu, A. Pely, A. Engstrom, H. Zhu, B.W. Brannigan, R. Kapur, S.L. Stott, T. Shioda, S. Ramaswamy, D.T. Ting, C.P. Lin, M. Toner, D.A. Haber, S. Maheswaran, Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis, Cell 158 (2014) 1110–1122.
[9] K.J. Cheung, V. Padmanaban, V. Silvestri, K. Schipper, J.D. Cohen, A.N. Fairchild, M.A. Gorin, J.E. Verdone, K.J. Pienta, J.S. Bader, A.J. Ewald, Polyclonal breast cancer metastases arise from collective dissemination of keratin 14-expressing tumor cell clusters, Proc. Natl. Acad. Sci. 113 (2016) E854–E863, https://doi.org/10.1073/pnas.1508541113.
[10] I. Pastushenko, A. Brisebarre, A. Sifrim, M. Fioramonti, T. Revenco, S. Boumahdi, A. Van Keymeulen, D. Brown, V. Moers, S. Lemaire, S. De Clercq, E. Minguijón, C. Balsat, Y. Sokolow, C. Dubois, F. De Cock, S. Scozzaro, F. Sopena, A. Lanas, N. D'Haene, I. Salmon, J.-C. Marine, T. Voet, P.A. Sotiropoulou, C. Blanpain, Identification of the tumour transition states occurring during EMT, Nature 556 (2018) 463–468, https://doi.org/10.1038/s41586-018-0040-3.
[11] M.K. Jolly, K.E. Ware, S. Gilja, J.A. Somarelli, H. Levine, EMT and MET: necessary or permissive for metastasis ? Mol. Oncol. 11 (2017) 755–769, https://doi.org/10.1002/1878-0261.12083.
[12] A.J. Armstrong, M.S. Marengo, S. Oltean, G. Kemeny, R.L. Bitting, J.D. Turnbull, C.I. Herold, P.K. Marcom, D.J. George, M.A. Garcia-Blanco, Circulating tumor cells from patients with advanced prostate and breast cancer display both epithelial and mesenchymal markers, Mol. Cancer Res. 9 (2011) 997–1007, https://doi.org/10.1158/1541-7786.MCR-10-0490.
[13] M. Yu, A. Bardia, B.S. Wittner, S.L. Stott, M.E. Smas, D.T. Ting, S.J. Isakoff, J.C. Ciciliano, M.N. Wells, A.M. Shah, K.F. Concannon, M.C. Donaldson, L.V. Sequist, E. Brachtel, D. Sgroi, J. Baselga, S. Ramaswamy, M. Toner, D.A. Haber, S. Maheswaran, Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition, Science 339 (2013) 580–584, https://doi.org/10.1126/science.1228522.
[14] M.K. Jolly, M. Boareto, B.G. Debeb, N. Aceto, M.C. Farach-Carson, W.A. Woodward, H. Levine, Inflammatory Breast Cancer: a model for investigating cluster-based dissemination, NPJ Breast Cancer 3 (2017) 21, https://doi.org/10.1101/119479.
[15] A.N. May, B.D. Crawford, A.M. Nedelcu, In vitro model-systems to understand the biology and clinical significance of circulating tumor cell clusters, Front. Oncol. 8 (2018) 9–12, https://doi.org/10.3389/fonc.2018.00063.
[16] A.F. Sarioglu, N. Aceto, N. Kojic, M.C. Donaldson, M. Zeinali, B. Hamza, A. Engstrom, H. Zhu, T.K. Sundaresan, D.T. Miyamoto, X. Luo, A. Bardia, B.S. Wittner, S. Ramaswamy, T. Shioda, D.T. Ting, S.L. Stott, R. Kapur, S. Maheswaran, D.A. Haber, M. Toner, A microfluidic device for label-free, physical capture of circulating tumor cell clusters, Nat. Methods 12 (2015) 685–691, https://doi.org/10.1038/nmeth.3404.
[17] M.J. Schliekelman, A. Taguchi, J. Zhu, X. Dai, J. Rodriguez, M. Celiktas, Q. Zhang, A. Chin, C. Wong, H. Wang, L. McFerrin, S. Selemat, C. Yang, E. Kroh, K. Garg, C. Behrens, A. Gazdar, J. Laird-Offringa, M. Tewari, J. Wistuba, J.P. Thiery, S.M. Hanash, Molecular portraits of epithelial, mesenchymal and hybrid states in lung adenocarcinoma and their relevance to survival, Cancer Res. 75 (2015) 1789–1800, https://doi.org/10.1158/0008-5472.CAN-14-2535.
[18] R.Y.-J. Huang, M.K. Wong, T.Z. Tan, K.T. Kuay, A.H.C. Ng, V.Y. Chung, Y.-S. Chu, N. Matsumura, H.-C. Lai, Y.F. Lee, W.-J. Sim, C. Chai, E. Pietschmann, S. Mori, J.J.H. Low, M. Choolani, J.P. Thiery, An EMT spectrum defines an anoikis-resistant and spheroidogenic intermediate mesenchymal state that is sensitive to e-cadherin restoration by a src-kinase inhibitor, saracatinib (AZD0530), Cell Death Dis. 4 (2013) e915, https://doi.org/10.1038/cddis.2013.442.
[19] S.S. Varankar, S.S. Kamble, A.M. Mali, M.M. More, A. Abraham, B. Kumar, K.J. Pansare, N.J. Narayanan, A. Sen, R.D. Dhake, A.N. Joshi, D. Midha, M. Jolly, Y. Dong, J.A. Clementa, S.A. Bapat, Functional balance between TCF21-slug defines phenotypic plasticity and sub-classes in high-grade serous ovarian cancer, BioRxiv (2018), https://doi.org/10.1101/307934.
[20] N. Harner-Foreman, J. Vadakekolathu, S.A. Laversin, M.G. Mathieu, S. Reeder, A.G. Pockley, R.C. Rees, D.J. Boocock, A novel spontaneous model of epithelial-mesenchymal transition (EMT) using a primary prostate cancer derived cell line demonstrating distinct stem-like characteristics, Sci. Rep. 7 (2017) 1–18, https://doi.org/10.1038/srep40633.
[21] J.T. George, M.K. Jolly, S. Xu, J.A. Somarelli, H. Levine, Survival outcomes in cancer patients predicted by a partial EMT gene expression scoring metric, Cancer Res. 77 (2017), https://doi.org/10.1158/0008-5472.CAN-16-3521.
[22] M.K. Jolly, M. Boareto, B. Huang, D. Jia, M. Lu, J.N. Onuchic, H. Levine, E. Ben-Jacob, Implications of the hybrid epithelial/mesenchymal phenotype in metastasis, Front. Oncol. 5 (2015), https://doi.org/10.3389/fonc.2015.00155.
[23] M. Lu, M.K. Jolly, H. Levine, J.N. Onuchic, E. Ben-Jacob, MicroRNA-based regulation of epithelial-hybrid-mesenchymal fate determination, Proc. Natl. Acad. Sci. 110 (2013) 18144–18149, https://doi.org/10.1073/pnas.1318192110.
[24] M.K. Jolly, S.C. Tripathi, D. Jia, S.M. Mooney, M. Celiktas, S.M. Hanash, S.A. Mani, K.J. Pienta, E. Ben-Jacob, H. Levine, Stability of the hybrid epithelial/mesenchymal phentoype, Oncotarget 7 (2016) 27067–27084.
[25] T. Hong, K. Watanabe, C.H. Ta, A. Villarreal-Ponce, Q. Nie, X. Dai, An Ovol2-Zeb1 mutual inhibitory circuit governs bidirectional and multi-step transition between epithelial and mesenchymal states, PLoS Comput. Biol. 11 (2015) e1004569, https://doi.org/10.1371/journal.pcbi.1004569.
[26] J. Zhang, X.J. Tian, H. Zhang, Y. Teng, R. Li, F. Bai, S. Elankumaran, J. Xing, TGF-β-induced epithelial-to-mesenchymal transition proceeds through stepwise activation of multiple feedback loops, Sci Signal 7 (2014) ra91, https://doi.org/10.1126/scisignal.2005304.
[27] B. De Craene, G. Berx, Regulatory networks defining EMT during cancer initiation

and progression, Nat. Rev. Cancer 13 (2013) 97–110, https://doi.org/10.1038/nrc3447.
[28] D. Schaeffer, J.A. Somarelli, G. Hanna, G.M. Palmer, M.A. Garcia-Blanco, Cellular migration and invasion uncoupled: increased migration is not an inexorable consequence of epithelial-to-mesenchymal transition, Mol. Cell. Biol. 34 (2014) 3486–3499, https://doi.org/10.1128/MCB.00694-14.
[29] S. Tanaka, W. Kobayashi, M. Haraguchi, K. Ishihata, N. Nakamura, M. Ozawa, Snail1 expression in human colon cancer DLD-1 cells confers invasive properties without N-cadherin expression, Biochem. Biophys. Rep. 8 (2016) 120–126, https://doi.org/10.1016/j.bbrep.2016.08.017.
[30] J.A. Somarelli, S. Shelter, M.K. Jolly, X. Wang, S. Bartholf Dewitt, A.J. Hish, S. Gilja, W.C. Eward, K.E. Ware, H. Levine, A.J. Armstrong, M.A. Garcia-Blanco, Mesenchymal-epithelial transition in sarcomas is controlled by the combinatorial expression of miR-200s and GRHL2, Mol. Cell. Biol. 36 (2016) 2503–2513, https://doi.org/10.1128/MCB.00373-16.
[31] S.J. Bidarra, P. Oliveira, S. Rocha, D.P. Saraiva, C. Oliveira, C.C. Barrias, A 3D in vitro model to explore the inter-conversion between epithelial and mesenchymal states during EMT and its reversion, Sci. Rep. 6 (2016) 27072, https://doi.org/10.1038/srep27072.
[32] Y. Chao, Q. Wu, M. Acquafondata, R. Dhir, A. Wells, Partial mesenchymal to epithelial reverting transition in breast and prostate cancer metastases, Cancer Microenviron. 5 (2012) 19–28, https://doi.org/10.1007/s12307-011-0085-4.
[33] E. Batlle, E. Sancho, C. Francí, D. Domínguez, M. Monfar, J. Baulida, A.G. De Herreros, The transcription factor snail is a repressor of E-cadherin gene expression in epithelial tumour cells, Nat. Cell Biol. 2 (2000) 84–89, https://doi.org/10.1038/35000034.
[34] A. Cano, M. A Pérez-Moreno, I. Rodrigo, A. Locascio, M.J. Blanco, M.G. del Barrio, F. Portillo, M. A Nieto, The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression, Nat. Cell Biol. 2 (2000) 76–83, https://doi.org/10.1038/35000025.
[35] K. Aigner, B. Dampier, L. Descovich, M. Mikula, A. Sultan, M. Schreiber, W. Mikulits, T. Brabletz, D. Strand, P. Obrist, W. Sommergruber, N. Schweifer, A. Wernitznig, H. Beug, R. Foisner, A. Eger, The transcription factor ZEB1 (deltaEF1) promotes tumour cell dedifferentiation by repressing master regulators of epithelial polarity, Oncogene 26 (2007) 6979–6988, https://doi.org/10.1038/sj.onc.1210508.
[36] J. Yang, S.A. Mani, J.L. Donaher, S. Ramaswamy, R. A Itzykson, C. Come, P. Savagner, I. Gitelman, A. Richardson, R.A. Weinberg, C. Val, A. Lamarque, Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis, Cell 117 (2004) 927–939, https://doi.org/10.1016/j.cell.2004.06.006.
[37] E. Beerling, D. Seinstra, E. de Wit, L. Kester, D. van der Velden, C. Maynard, R. Schäfer, P. van Diest, E. Voest, A. van Oudenaarden, N. Vrisekoop, J. van Rheenen, Plasticity between epithelial and mesenchymal states unlinks EMT from metastasis-enhancing stem cell capacity, Cell Rep. 14 (2016) 2281–2288, https://doi.org/10.1016/j.celrep.2016.02.034.
[38] C.T. Guy, R.D. Cardiff, W.J. Muller, Induction of mammary tumors by expression of polyomavirus middle T oncogene: a transgenic mouse model for metastatic disease, Mol. Cell. Biol. 12 (1992) 954–961, https://doi.org/10.1128/MCB.12.3.954.
[39] K.V. Nguyen-Ngoc, K.J. Cheung, A. Brenot, E.R. Shamir, R.S. Gray, W.C. Hines, P. Yaswen, Z. Werb, A.J. Ewald, ECM microenvironment regulates collective migration and local dissemination in normal and malignant mammary epithelium, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) E2595–E2604, https://doi.org/10.1073/pnas.1212834109.
[40] X. Zheng, J.L. Carstens, J. Kim, M. Scheible, J. Kaye, H. Sugimoto, C.-C. Wu, V.S. Lebleu, R. Kalluri, Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer, Nature 527 (2015) 525–530, https://doi.org/10.1038/nature16064.
[41] K.R. Fischer, A. Durrans, S. Lee, J. Sheng, F. Li, S.T.C. Wong, H. Choi, T. El Rayes, S. Ryu, J. Troeger, R.F. Schwabe, L.T. Vahdat, N.K. Altorki, V. Mittal, D. Gao, Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance, Nature 527 (2015) 472–476, https://doi.org/10.1038/nature15748.
[42] N.M. Aiello, T. Brabletz, Y. Kang, A.M. Nieto, R.A. Weinberg, B.Z. Stagner, Upholding a role for EMT in pancreatic cancer metastasis, Nature 547 (2017) E7–E8, https://doi.org/10.1038/nature16064.
[43] X. Ye, T. Brabletz, Y. Kang, G.D. Longmore, M.A. Nieto, B.Z. Stagner, J. Yang, R.A. Weinberg, Upholding a role for EMT in breast cancer metastasis, Nature 547 (2017) E1–E3, https://doi.org/10.1038/nature15748.
[44] S.A. Mani, W. Guo, M.-J. Liao, E.N. Eaton, A. Ayyanan, A.Y. Zhou, M. Brooks, F. Reinhard, C.C. Zhang, M. Shipitsin, L.L. Campbell, K. Polyak, C. Brisken, J. Yang, R.A. Weinberg, The epithelial-mesenchymal transition generates cells with properties of stem cells, Cell 133 (2008) 704–715, https://doi.org/10.1016/j.cell.2008.03.027.
[45] Z. Wang, Y. Li, D. Kong, S. Banerjee, A. Ahmad, A.S. Azmi, S. Ali, J.L. Abbruzzese, G.E. Gallick, F.H. Sarkar, Acquisition of epithelial-mesenchymal transition phenotype of gemcitabine-resistant pancreatic cancer cells is linked with activation of the notch signaling pathway, Cancer Res. 69 (2009) 2400–2407, https://doi.org/10.1158/0008-5472.CAN-08-4312.
[46] A. Grosse-Wilde, A. Fouquier D' Herouel, E. McIntosh, G. Ertaylan, A. Skupin, R.E. Kuestner, A. del Sol, K.-A. Walters, S. Huang, Stemness of the hybrid epithelial/mesenchymal state in breast cancer and its association with poor survival, PLoS One 10 (2015) e0126522, https://doi.org/10.1371/journal.pone.0126522.
[47] A. Goldman, B. Majumder, A. Dhawan, S. Ravi, D. Goldman, M. Kohandel, P.K. Majumder, S. Sengupta, Temporally sequenced anticancer drugs overcome adaptive resistance by targeting a vulnerable chemotherapy-induced phenotypic transition, Nat. Commun. 6 (2015) 6139, https://doi.org/10.1038/ncomms7139.
[48] B. Bierie, S.E. Pierce, C. Kroeger, D.G. Stover, D.R. Pattabiraman, P. Thiru, J. Liu Donaher, F. Reinhardt, C.L. Chaffer, Z. Keckesova, R.A. Weinberg, Integrin-β4 identifies cancer stem cell-enriched populations of partially mesenchymal carcinoma cells, Proc. Natl. Acad. Sci. 114 (2017) E2337–E2346, https://doi.org/10.1073/pnas.1618298114.
[49] M. Ruscetti, B. Quach, E.L. Dadashian, D.J. Mulholland, W. Hong, Tracking and functional characterization of epithelial-mesenchymal transition and mesenchymal tumor cells during prostate cancer metastasis, Cancer Res. 75 (2015) 2749–2759, https://doi.org/10.1158/0008-5472.CAN-14-3476.
[50] J.M. Schmidt, E. Panzilius, H.S. Bartsch, M. Irmler, J. Beckers, V. Kari, J.R. Linnemann, D. Dragoi, B. Hirschi, U.J. Kloos, S. Sass, F. Theis, S. Kahlert, S.A. Johnsen, K. Sotlar, C.H. Scheel, Stem-cell-like properties and epithelial plasticity arise as stable traits after transient Twist1 activation, Cell Rep. 10 (2015) 131–139, https://doi.org/10.1016/j.celrep.2014.12.032.
[51] H.D. Tran, K. Luitel, M. Kim, K. Zhang, G.D. Longmore, D.D. Tran, Transient SNAIL1 expression is necessary for metastatic competence in breast cancer, Cancer Res. 74 (2014) 6330–6340.
[52] O.H. Ocaña, R. Córcoles, A. Fabra, G. Moreno-Bueno, H. Acloque, S. Vega, A. Barrallo-Gimeno, A. Cano, M.A. Nieto, Metastatic colonization requires the repression of the epithelial-mesenchymal transition inducer Prrx1, Cancer Cell 22 (2012) 709–724, https://doi.org/10.1016/j.ccr.2012.10.012.
[53] M.K. Jolly, D. Jia, M. Boareto, S.A. Mani, K.J. Pienta, E. Ben-Jacob, H. Levine, Coupling the modules of EMT and stemness: a tunable "stemness window" model, Oncotarget (6) (2015), https://doi.org/10.18632/oncotarget.4629.
[54] J. Varga, F.R. Greten, Cell plasticity in epithelial homeostasis and tumorigenesis, Nat. Cell Biol. 19 (2017) 1133–1141, https://doi.org/10.1038/ncb3611.
[55] F. Bocci, M.K. Jolly, J.T. George, H. Levine, J.N. Onuchic, A mechanism-based computational model to capture the interconnections among epithelial-mesenchymal transition, cancer stem cells, and notch-jagged signaling, Oncotarget. (2018), https://doi.org/10.18632/oncotarget.25692.
[56] J.A. Colacino, E. Azizi, M.D. Brooks, R. Harouaka, S. Fouladdel, S.P. McDermott, M. Lee, D. Hill, J. Madde, J. Boerner, M.L. Cote, M.A. Sartor, L.S. Rozek, M.S. Wicha, Heterogeneity of human breast stem and progenitor cells as revelaed by transcriptional profiling, Stem Cell Rep. 10 (2018) 1596–1609, https://doi.org/10.1016/j.stemcr.2016.05.008.
[57] S. Liu, Y. Cong, D. Wang, Y. Sun, L. Deng, Y. Liu, R. Martin-Trevino, L. Shang, S.P. McDermott, M.D. Landis, S. Hong, A. Adams, R. D'Angelo, C. Ginestier, E. Charafe-Jauffret, S.G. Clouthier, D. Birnbaum, S.T. Wong, M. Zhan, J.C. Chang, M.S. Wicha, Breast cancer stem cells transition between epithelial and mesenchymal states reflective of their normal counterparts, Stem Cell Rep. 2 (2014) 78–91, https://doi.org/10.1016/j.stemcr.2013.11.009.
[58] M.K. Jolly, B. Huang, M. Lu, S.A. Mani, H. Levine, E. Ben-Jacob, Towards elucidating the connection between epithelial–mesenchymal transitions and stemness, J. R. Soc. Interface 11 (2014) 20140962, https://doi.org/10.1098/rsif.2014.0962.
[59] M. Ruscetti, E.L. Dadashian, W. Guo, B. Quach, D.J. Mulholland, J.W. Park, L.M. Tran, N. Kobayashi, D. Bianchi-Frias, Y. Xing, P.S. Nelson, H. Wu, HDAC inhibition impedes epithelial-mesenchymal plasticity and suppresses metastatic, castration-resistant prostate cancer, Oncogene 35 (2016) 3781–3795, https://doi.org/10.1038/onc.2015.444.
[60] J.A. Somarelli, D. Schaeffer, M.S. Marengo, T. Bepler, D. Rouse, K.E. Ware, A.J. Hish, Y. Zhao, A.F. Buckley, J.I. Epstein, A.J. Armstrong, D.M. Virshup, M.A. Garcia-Blanco, Distinct routes to metastasis: plasticity-dependent and plasticity-independent pathways, Oncogene 35 (2016) 4302–4311, https://doi.org/10.1038/onc.2015.497.
[61] K.J. Cheung, A.J. Ewald, Illuminating breast cancer invasion: diverse roles for cell-cell interactions, Curr. Opin. Cell Biol. 30 (2014) 99–111, https://doi.org/10.1016/j.ceb.2014.07.003.
[62] J. Caramel, M. Ligier, A. Puisieux, Pleiotropic roles for ZEB1 in cancer, Cancer Res. 78 (2018) 30–35, https://doi.org/10.1158/0008-5472.CAN-17-2476.
[63] S. Goossens, N. Vandamme, P. Van Vlierberghe, G. Berx, EMT transcription factors in cancer development re-evaluated: beyond EMT and MET, Biochim. Biophys. Acta 1868 (2017) 584–591, https://doi.org/10.1016/j.bbcan.2017.06.006.
[64] M. Pietilä, J. Ivaska, S.A. Mani, Whom to blame for metastasis, the epithelial–mesenchymal transition or the tumor microenvironment? Cancer Lett. 380 (2016) 359–368, https://doi.org/10.1016/j.canlet.2015.12.033.
[65] D.H. Peng, C. Ungewiss, P. Tong, L.A. Byers, J. Wang, J.R. Canales, P.A. Villalobos, N. Uraoka, B. Mino, C. Behrens, I.I. Wistuba, R.I. Han, C.A. Wanna, M. Fahrenholtz, K.J. Grande-Allen, C.J. Creighton, D.L. Gibbons, ZEB1 induces LOXL2-mediated collagen stabilization and deposition in the extracellular matrix to drive lung cancer invasion and metastasis, Oncogene 36 (2016) 1925–1938, https://doi.org/10.1038/onc.2016.358.
[66] S.C. Wei, L. Fattet, J.H. Tsai, Y. Guo, V.H. Pai, H.E. Majeski, A.C. Chen, R.L. Sah, S.S. Taylor, A.J. Engler, J. Yang, Matrix stiffness drives epithelial–mesenchymal transition and tumour metastasis through a TWIST1–G3BP2 mechanotransduction pathway, Nat. Cell Biol. 17 (2015) 678–688, https://doi.org/10.1038/ncb3157.
[67] B.-T. Preca, K. Bajdak, K. Mock, W. Lehmann, V. Sundararajan, P. Bronsert, A. Matzge-Ogi, V. Orian-Rousseau, S. Brabletz, T. Brabletz, J. Maurer, M.P. Stemmler, A novel ZEB1/HAS2 positive feedback loop promotes EMT in breast cancer, Oncotarget 8 (2017) 11530–11543, https://doi.org/10.18632/oncotarget.14563.
[68] M.K. Jolly, B.-T. Preca, S.C. Tripathi, D. Jia, S.M. Hanash, T. Brabletz, M.P. Stemmler, J. Maurer, H. Levine, Interconnected feedback loops among ESRP1, HAS2, and CD44 regulate epithelial-mesenchymal plasticity in cancer, BioRxiv, (2018), https://doi.org/10.1101/260349.
[69] D. Neelakantan, H. Zhou, M.U.J. Oliphant, X. Zhang, L.M. Simon, D.M. Henke, C.A. Shaw, M.F. Wu, S.G. Hilsenbeck, L.D. White, M.T. Lewis, H.L. Ford, EMT cells

increase breast cancer metastasis via paracrine GLI activation in neighbouring tumour cells, Nat. Commun. 8 (2017) 15773, https://doi.org/10.1038/ncomms15773.
[70] T. Tsuji, S. Ibaragi, K. Shima, M.G. Hu, M. Katsurano, A. Sasaki, G.F. Hu, Epithelial-mesenchymal transition induced by growth suppressor p12 CDK2-AP1 promotes tumor cell local invasion but suppresses distant colony growth, Cancer Res. 68 (2008) 10377–10386, https://doi.org/10.1158/0008-5472.CAN-08-1444.
[71] A. Grosse-Wilde, R.E. Kuestner, S.M. Skelton, E. MacIntosh, A. Fouquier D' Herouei, G. Ertaylan, A. del Sol, A. Skupin, S. Huang, Loss of inter-cellular cooperation by complete epithelial-mesenchymal transition supports favorable outcomes in basal breast cancer patients, Oncotarget 9 (2018) 20018–20033.
[72] S.C. Tripathi, H.L. Peters, A. Taguchi, H. Katayama, H. Wang, A. Momin, M.K. Jolly, M. Celiktas, J. Rodriguez-Canales, H. Liu, C. Behrens, I.I. Wistuba, E. Ben-Jacob, H. Levine, J.J. Molldrem, S.M. Hanash, E.J. Ostrin, Immunoproteasome deficiency is a feature of non-small cell lung cancer with a mesenchymal phenotype and is associated with a poor outcome, Proc. Natl. Acad. Sci. 113 (2016) E1555–E1564, https://doi.org/10.1073/pnas.1521812113.
[73] A.N. Paranjape, R. Soundararajan, S.J. Werden, R. Joseph, J.H. Taube, H. Liu, J. Rodriguez-Canales, N. Sphyris, I. Wistuba, N. Miura, J. Dhillon, N. Mahajan, K. Mahajan, J.T. Chang, M. Ittmann, S.N. Maity, C. Logothetis, D.G. Tang, S.A. Mani, Inhibition of FOXC2 restores epithelial phenotype and drug sensitivity in prostate cancer cells with stem-cell properties, Oncogene 35 (2016) 5963–5976, https://doi.org/10.1038/onc.2015.498.
[74] P. Zhang, Y. Wei, L.i. Wang, B.G. Debeb, Y. Yuan, J. Zhang, J. Yuan, M. Wang, D. Chen, Y. Sun, W.A. Woodward, Y. Liu, D.C. Dean, H. Liang, Y. Hu, K.K. Ang, M.C. Hung, J. Chen, L. Ma, ATM-mediated stabilization of ZEB1 promotes DNA damage response and radioresistance through CHK1, Nat. Cell Biol. 16 (2014) 864–875, https://doi.org/10.1038/ncb3013.
[75] A.M. Krebs, J. Mitschke, M.L. Losada, O. Schmalhofer, M. Boerries, H. Busch, M. Boettcher, D. Mougiakakos, W. Reichardt, P. Bronsert, V.G. Brunton, C. Pilarsky, T.H. Winkler, S. Brabletz, M.P. Stemmler, The EMT-activator Zeb1 is a key factor for cell plasticity and promotes metastasis in pancreatic cancer, Nat. Cell Biol. 19 (2017) 518–529, https://doi.org/10.1038/ncb3513.
[76] J. Kanska, P.-J.P. Aspuria, B. Taylor-Harding, L. Spurka, V. Funari, S. Orsulic, B.Y. Karlan, W.R. Wiedemeyer, Glucose deprivation elicits phenotypic plasticity via ZEB1-mediated expression of NNMT, Oncotarget 8 (2017) 26200–26220, https://doi.org/10.18632/oncotarget.15429.
[77] M. Masin, J. Vazquez, S. Rossi, S. Groeneveld, N. Samson, P.C. Schwalie, B. Deplancke, L.E. Frawley, J. Gouttenoire, D. Moradpour, T.G. Oliver, E. Meylan, GLUT3 is induced during epithelial-mesenchymal transition and promotes tumor cell proliferation in non-small cell lung cancer, Cancer Metab. 2 (2014) 11, https://doi.org/10.1186/2049-3002-2-11.
[78] H. Wang, B. Huang, B. Mou, L. Kai, Y. Cao, C. Qiang, S. Jian, J. Jin, C. Pan, Z. Ren, W. Huan, Y. Lin, D. Hu, W. Shao, P. Qiu, ZEB1-mediated vasculogenic mimicry formation associates with epithelial – mesenchymal transition and cancer stem cell phenotypes in prostate cancer, (2018) 1–14. doi:https://doi.org/10.1111/jcmm.13637.
[79] S. Brabletz, T. Brabletz, The ZEB/miR-200 feedback loop–a motor of cellular plasticity in development and cancer? EMBO Rep. 11 (2010) 670–677, https://doi.org/10.1038/embor.2010.117.
[80] J. Massagué, A.C. Obenauf, Metastatic colonization by circulating tumour cells, Nature 529 (2016) 298–306, https://doi.org/10.1038/nature17038.
[81] X.-K. Qi, H.-Q. Han, H.-J. Zhang, M. Xu, L. Li, L. Chen, T. Xiang, Q.-S. Feng, T. Kang, C.-N. Qian, M.-Y. Cai, Q. Tao, Y.-X. Zeng, L. Feng, OVOL2 links stemness and metastasis via fine-tuning epithelial-mesenchymal transition in nasopharyngeal carcinoma, Theranostics 8 (2018) 2202–2216, https://doi.org/10.7150/thno.24003.
[82] F. Andriani, G. Bertolini, F. Facchinetti, E. Baldoli, M. Moro, P. Casalini, R. Caserini, M. Milione, G. Leone, G. Pelosi, U. Pastorino, G. Sozzi, L. Roz, Conversion to stem-cell state in response to microenvironmental cues is regulated by balance between epithelial and mesenchymal features in lung cancer cells, Mol. Oncol. 10 (2016) 253–271, https://doi.org/10.1016/j.molonc.2015.10.002.
[83] V.L. Battula, K.W. Evans, B.G. Hollier, Y. Shi, F.C. Marini, A. Ayyanan, R.Y. Wang, C. Brisken, R. Guerra, M. Andreeff, S.A. Mani, Epithelial-mesenchymal transition-derived cells exhibit multilineage differentiation potential similar to mesenchymal stem cells, Stem Cells 28 (2010) 1435–1445, https://doi.org/10.1002/stem.467.
[84] T.Z. Tan, Q.H. Miow, Y. Miki, T. Noda, S. Mori, R.Y. Huang, J.P. Thiery, Epithelial-mesenchymal transition spectrum quantification and its efficacy in deciphering survival and drug responses of cancer patients, EMBO Mol. Med. 6 (2014) 1279–1293, https://doi.org/10.15252/emmm.201404208.
[85] V. Fustaino, D. Presutti, T. Colombo, B. Cardinali, G. Papoff, R. Brandi, P. Bertolazzi, G. Felici, G. Ruberti, Characterization of epithelial-mesenchymal transition intermediate/hybrid phenotypes associated to resistance to EGFR inhibitors in non-small cell lung cancer cell lines, Oncotarget 8 (2017) 103340–103363, https://doi.org/10.18632/oncotarget.21132.
[86] A. Biddle, L. Gammon, X. Liang, D.E. Costea, I.C. Mackenzie, Phenotypic plasticity determines cancer stem cell therapeutic resistance in oral squamous cell carcinoma, EBioMedicine 4 (2016) 138–145, https://doi.org/10.1016/j.ebiom.2016.01.007.
[87] S. Lovisa, V.S. Lebleu, B. Tampe, H. Sugimoto, K. Vadnagara, J.L. Carstens, C.-C. Wu, Y. Hagos, B.C. Burckhardt, T. Pentcheva-Hoang, H. Nischal, J.P. Allison, M. Zeisberg, R. Kalluri, Epithelial-to-mesenchymal transition induces cell cycle arrest and parenchymal damage in renal fibrosis, Nat. Med. 21 (2015) 998–1009, https://doi.org/10.1038/nm.3902.
[88] S. Vega, A.V. Morales, O.H. Ocaña, F. Valdés, I. Fabregat, M.A. Nieto, Snail blocks the cell cycle and confers resistance to cell death, Genes Dev. 18 (2004) 1131–1143, https://doi.org/10.1101/gad.294104.
[89] J. Handler, J. Cullis, A. Avanzi, E.A. Vucic, Pre-neoplastic pancreas cells enter a partially mesenchymal state following transient TGF-β exposure, Oncogene (2018), https://doi.org/10.1038/s41388-018-0264-6.
[90] M. Boareto, M.K. Jolly, A. Goldman, M. Pietila, S.A. Mani, S. Sengupta, E. Ben-Jacob, H. Levine, J.N. Onuchic, Notch-jagged signaling can give rise to clusters of cells exhibiting a hybrid epithelial/mesenchymal phenotype, J. R. Soc. Interface 13 (2016) 20151106, https://doi.org/10.1098/rsif.2015.1106.
[91] M. Giuliano, A. Shaikh, H.C. Lo, G. Arpino, S. De Placido, X.H. Zhang, M. Cristofanilli, R. Schiff, M.V. Trivedi, Perspective on circulating tumor cell clusters: why it takes a village to metastasize, Cancer Res. 78 (2018) 845–852, https://doi.org/10.1158/0008-5472.CAN-17-2748.
[92] T. Wang, G. Liu, R. Wang, The intercellular metabolic interplay between tumor and immune cells, Front. Immunol. 5 (2014) 1–7, https://doi.org/10.3389/fimmu.2014.00358.
[93] B.A. Camley, J. Zimmermann, H. Levine, W.J. Rappel, Collective signal processing in cluster chemotaxis: roles of adaptation, amplification, and co-attraction in collective guidance, PLoS Comput. Biol. 12 (2016) 1–28, https://doi.org/10.1371/journal.pcbi.1005008.
[94] S. Al Habyan, C. Kalos, J. Szymborski, L. McCaffrey, Multicellular detachment generates metastatic spheroids during intra-abdominal dissemination in epithelial ovarian cancer, Oncogene (2018), https://doi.org/10.1038/s41388-018-0317-x.
[95] M. Mandal, B. Ghosh, A. Anura, P. Mitra, T. Pathak, J. Chatterjee, Modeling continuum of epithelial mesenchymal transition plasticity, Integr. Biol. 8 (2016) 167–176, https://doi.org/10.1039/C5IB00219B.
[96] M.K. Jolly, P. Kulkarni, K. Weninger, J. Orban, H. Levine, Phenotypic plasticity, bet-hedging, and androgen independence in prostate cancer: role of non-genetic heterogeneity, Front. Oncol. 8 (2018) 50, https://doi.org/10.3389/fonc.2018.00050.
[97] M.K. Jolly, et al., E-cadherin represses anoikis resistance in sarcomas through both signaling and mechanical mechanisms, bioRxiv (2018), https://doi.org/10.1101/347815.
[98] D. van Dijk, K. Yim, R. Sharma, J. Nainyas, P. Kathail, et al., Recovering Gene Interactions from Single-Cell Data Using Data Diffusion, (2018), https://doi.org/10.1016/j.cell.2018.05.061.
[99] Sidharth V. Puram, I. Tirosh, Anuraag S. Parikh, Anoop P. Patel, Derrick T. Lin, A. Regev, Bradley E. Bernstein, et al., Single-cell transcriptomic analysis of primary and metastatic tumour ecosystem in head and neck cancer, Cell 171 (7) (2017) P1611–P1624, https://doi.org/10.1016/j.cell.2017.10.044 e24.